

## REMARKS

### Additional Claims

Applicants request that when the composition claims of the present invention are found patentable, newly added method claims 9 and 10 are examined through the rejoinder procedure in accordance with MPEP §821.04. When an application as originally filed discloses a product and the process for making and/or using such product, and only the claims directed to the product are presented for examination, when a product claim is found allowable, applicant may present claims directed to the process of making and/or using the patentable product for examination through rejoinder procedure in accordance with MPEP §821.04, provided that the process claims depend from or include all the limitations of the allowed product claims.

In the present application the product claims 1, 2, 6 and 8 are directed to a composition and new claims 9 and 10 are directed to a method for using the compositions. Applicants, therefore, request the Office to take up the method claims for examination when product claims 1, 2, 6 and 8 are allowed.

### Rejection of Claims and Traversal Thereof

In the March 28, 2003 Office Action,

claims 1 and 6 were rejected under 35 U.S.C. §112, second paragraph;

claims 1, 2-4 and 6 were rejected under 35 U.S.C. §112, first paragraph; and

claims 1, 2-4 and 6 were rejected under 35 U.S.C. §102(b) as being anticipated by Drzeniek, et al. (Cancer Letter 56: 173-179, 1991); Prall, et al. (The Journal of Histochemistry and Cytochemistry 44: 35-41 1996); Draberova, et al. (Folia Biologica 43: 343, 1997, PTO 892 #5) or Blumberg (U.S. Patent publication US 2002/0028203, with priority to 4/15/98).

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

**Rejection under 35 U.S.C. §112, second paragraph**

In the March 28, 2003 Office Action, claims 1 and 6 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended claims 1 and 6, thereby obviating the rejection. Withdrawal of this rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

**Rejection under 35 U.S.C. §112, first paragraph**

Claims 1-2 and 6 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has amended independent claim 1, thereby obviating the rejection. Withdrawal of this rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Claim 4 was rejected under 35 U.S.C. §112, first paragraph because, according to the Office, evidence has not been provided that the claimed biological material is known and readily available to the public. Applicants have requested a copy of the Certification of the Availability, but to date has not been received. Applicants will submit in the near future.

Claims 1-4 and 6 were rejected under 35 U.S.C. §112, first paragraph, because according to the Office, the specification, while being enabling for a composition comprising an **anti-CD66a antibody or the antibody 4D1/C2** with successful completion of the deposit requirement, does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants vigorously disagree. To demonstrate the lack of enablement, the Office must demonstrate that one of skilled in the art cannot, without undue experimentation, make and/or use the claimed compositions and their corresponding therapies to inhibit the formation of capillaries. Further, even if some experimentation may be involved in practicing the invention, it is well settled that the enablement requirement permits some experimentation, so long as that experimentation is not undue. In *PPG Indus., Inc., v. Guardian Indus. Corp.*, 27 USPQ2d 1618, 1623 (Fed. Cir. 1996), the court stated that even where some experimentation is necessary to reduce an invention to practice, the enablement requirement is

satisfied where: (1) the experimentation is routine; or (2) the specification provides "a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. Applicants' specification meets these guidelines.

Applicants have amended the claims to recite an enabling antibody, as stated by the Office, namely the **anti-CD66a 4D1/C2 antibody**. Thus, the applicants' disclosure enables one skilled in the art to obtain, without undue experimentation, the claimed compositions of the present invention.

According to the Office:

"The claims as written as drawn to pharmaceutical compositions which read on *in vivo* treatment for cancer. However, the data presented to support the enablement of the claims is based on cell culture, *in vitro* studies. One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between inhibition of CD66a and tumor angiogenesis *in vivo*"

Applicants vigorously disagree. Initially, applicants remind the Office that the standard for enablement and thus patentability is not the same as that required for drug marketing approval by the Federal Drug Administration. See *Scott v. Finney*, 32 USPQ2d 115 (Fed. Cir. 1994). The Office has faulted the applicants for not providing *in vivo* examples to show the efficacy of the claimed invention. Applicants submit that the efficacy of the compositions of this invention is fully and rigorously established by applicants' empirical determinations — applicants tested the efficacy of the claimed compositions *in vitro* to determine the positive results showing inhibition of angiogenesis.

According to the Office, a 1983 reference (Freshney, Culture of Animal Cells) teaches that there are many differences between cultured cells and their counterparts *in vivo*. Specifically, the reference discusses that many culture environments lack the input of the nervous and endocrine system involved in homeostatic regulation *in vivo*. It should be noted that applicants took further steps to ensure that the culture form represented *in vivo* conditions, as discussed at page 11, paragraph [0046] of the specification. For example, the cells were cultured in the presence of specific growth factors such as VEGF (vascular endothelial growth factor) or FGF-2 (fibroblast growth factor) in a connective tissue matrix, which provides similar growth behavior as *in vivo* conditions.

The Freshney reference further alleges that the differences stem from the dissociation of cells from a three dimensional geometry and their propagation on a two-dimensional substrate. Applicants remind the Office that great strides have been made regarding culturing of cells from the 1983 publication date of Freshney. Clearly, the present specification teaches that the cells were cultured in three-dimensional collagen I gels (see page 11, paragraph [0047]) and thus the required three dimensional control to show the directional capillary sprouting or lack thereof was easily demonstrated. Clearly, the concerns raised twenty years ago regarding culture conditions by Freshney are no longer relevant with the technology available at the time of filing of the present invention.

The Office then cited an article<sup>2</sup> by Gura that discussed the unpredictability of drug discovery for cancer therapy. However, it should be noted that the reference expressly states at page 1042, column 1, that:

“The limitation of animal models have spurred the NCI, among others, to test drug candidate in cultures of human cells. The institute now relies on a panel of 60 human cells, including samples of all the major human malignances. Drugs to be tested are fed to subsets of the panel, based on tumor cell type, and their cell-killing activity is monitored.”

Thus, it is evident that the NCI, cited as an authority by the Office, also considers the use of cancer cells as an appropriate and applicable testing method for cancer treatments. Thus applicants have completed testing within the guidelines recommended by NCI.

The claims as now amended recite applicants' invention in terms fully supported in the disclosure defining the subject matter sought to be patented. The claims thus are in compliance with the enablement requirement of the first paragraph of section 112. Applicants respectfully request the withdrawal of the rejection of claims 1-4 and 6 under §112, first paragraph.

#### **Rejection under 35 U.S.C. §102(b)**

Claims 1, 2-4 and 6 were rejected under 35 U.S.C. §102(b) as being anticipated by Drzeniek, et al.; Prall, et al.; Draberova, et al.; or Blumberg. Applicants respectfully traverse this rejection and submit that the claims, as now amended, are not anticipated by any of the cited references.

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<sup>2</sup> Gura, Trisha, System for Identifying New Drugs Are Often Faulty, *Science*, Vol. 276, November 7, 1997.

Anticipation under 35 U.S.C. §102 requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."<sup>3</sup> The cited references do not meet this standard.

Applicants' amended claim 1 reads as follows:

1. A pharmaceutical composition for inhibiting angiogenesis, comprising monoclonal anti-CD66a 4D1/C2 antibody which was deposited with DSMZ (German-Type Collection of Microorganisms and Cell Cultures) Braunschweig under DSM ACC2371 on October 22, 1998, wherein the monoclonal anti-CD66a 4D1/C2 antibody is in an effective amount to inhibit formation of capillaries by functionally blocking CD66a.

Neither the Draberova, et al. reference nor the Blumberg reference in anyway disclose, teach or suggest the use of the monoclonal anti-CD66a 4D1/C2 antibody as recited in applicants' claimed invention. Moreover, the cited references do not disclose, teach or suggest the use the claimed antibody in an effective amount to inhibit formation of capillaries by functionally blocking CD66a. Thus, neither reference is anticipatory of the applicants' claimed invention.

The Office further cites Drzeniek, et al. and Prall, et al., as anticipatory of applicants' claimed invention. Applicants' claimed invention recites the use of monoclonal anti-CD66a 4D1/C2 antibody in a composition. This specific antibody was deposited, in secret, with DSMZ (German-Type Collection of Microorganisms and Cell Cultures) Braunschweig under DSM ACC2371 on October 22, 1998.

According to the Office, the claimed antibodies are disclosed in both the Drzeniek, et al. and Prall, et al. references. Applicants vigorously disagree because neither reference clearly shows that the disclosed 4D1/C2 antibodies in the respective references are the same when compared to each other or whether the disclosed antibodies are the same as the presently claimed antibody. Drzeniek, et al, discusses three specific antigens having a molecular weight of 85,000; 115,000 or 170,000. The Drzeniek, et al, reference clearly stated that the discussed MAb 4D1/C2 antibody binds preferentially to the antigen of  $M_r$  85,000. It should be noted that there was no binding to an antigen of  $M_r$  170,000 (see page 177, top of column 2). In contrast, the MAb 4D1/C2 discussed in the Prall, et al. reference binds to an antigen having a  $M_r$  of 160,000. It is apparent that the two cited references disclose two separate and distinct monoclonal antibodies that may have the same name but certainly do not bind to the same antigen.

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<sup>3</sup> Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicants question as to which one of the cited reference is anticipatory. Each reference is vague and uncertain to such an extent as to beg the question of whether either reference is enabling because of the fundamental ambiguities that are introduced when comparing the two references. It is well established as a matter of law that before a reference can be prior art under section 102, a reference must be enabling and it must put the claimed invention in the hands of one skilled in the art. (*In re Sun*, 31 USPQ2d 1451 (Fed. Cir. 1993)). At this point, applicants submit that neither reference puts the claimed invention in the hand of one skilled in the art.

Further, it is well established that a rejection on the grounds of anticipation cannot be predicated on an ambiguous reference *In re Turlay*, 49 CCPA 1288, 134 USPQ 355, 360 (CCPA 1962) citing *In re Cramblet*, 20 CCPA 755, 62 F.2d 358, 16 USPQ 47, 75-76:

“Statement in a prior application relied on to prove anticipation must be so clear and explicit that those skilled in the art will have no difficulty in ascertaining their meaning. Where they are so vague, involved, intricate, and **contradictory** (emphasis added) that experts disagree radically as to their meaning...it is safe to reject such a document as anticipation.”

Thus, a reference is good for only that which it clearly and definitely discloses. Further, if a reference is ambiguous and can be interpreted so that it may or may not constitute an anticipation of an applicant's claim, an anticipation rejection under 35 U.S.C. §102 based upon the ambiguous reference is improper (*In re Hughes*, 145 USPQ 467 (CCPA 1965)). This is the current situation, and as such, neither reference supports an anticipation rejection.

Still further, neither reference in anyway discloses, teaches, or suggests the use of the presently claimed antibody in an effective amount to inhibit or reduce formation of capillaries by functionally blocking CD66a, nor can it be implied that this event inherently occurs. First, inherency cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *In re Oelrich*, 212 USPQ 323 (CCPA 1981). Instead, it must consistently occur each and every time, which is necessary under case law to prove inherency.

Furthermore, are the Drzeniek, et al., and Prall, et al. references so clear and explicit that one skilled in the art will have no difficulty in ascertaining what is disclosed? Applicants contend that the references **are not clear and explicit**, in fact, the exact binding of the discussed antibodies to which antigen is uncertain because of the ambiguous and seemingly contradictory statements in the Drzeniek, et al. and Prall, et al. references.

Accordingly, applicants respectfully submit that claims 1-4 and 6, as amended, are patentably distinguishable over Drzeniek, et al. and Prall, et al. Withdrawal of this rejection under 35 U.S.C. §102(b) is requested.

#### **Priority Application**

The present application was filed under 35 U.S.C. §371 as evidenced by the enclosed Notice of Acceptance under 35 USC §371 (Appendix A). Thus, a copy of the certified copy of the priority document was received in the national stage application from the International Bureau (PCT Rule 17.2(a)) and applicants should not be required to submit another copy.

#### **Petition for Extension of Time/Fees Payable**

Applicants hereby petitions for a three (3) month extension of time, extending the deadline for responding to the March 28, 2003 Office Action from June 28, 2003 to September 28, 2003. The entry of this petition results in a petition fee of \$465.00. Applicants have added three new claims, however the inclusion of these claims do not go beyond the number for which a fee has previously been paid, and as such, no additional fee is required. A check in the amount of \$465.00 is submitted herewith in payment of the petition fee for a three-month extension. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

#### **Conclusion**

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Helms reconsider the patentability of claims 1, 2, 4, 6 and 8-10 in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Helms is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,



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